

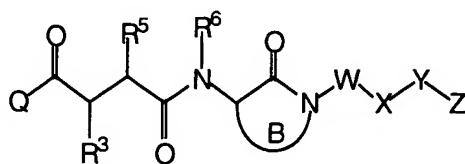
CLAIMS

What is claimed is:

- 5 1. A method of screening for inhibitors of beta-amyloid
production comprising,
- 10 1) contacting a potential inhibitor of beta-amyloid
production and a tagged inhibitor of beta-amyloid
production with at least one macromolecule involved
in the processing of APP and the production of beta-
amyloid peptide, said macromolecule containing a
binding site specific for said tagged inhibitor of
beta-amyloid production;
- 15 2) separating the tagged inhibitor of beta-amyloid
production bound to said macromolecule from the
tagged inhibitor of beta-amyloid production free
from said macromolecule; and
- 20 3) determining an inhibitory concentration of the
potential inhibitor of beta-amyloid production from
the concentration of tagged inhibitor of beta-
amyloid production bound to said macromolecule.
- 25 2. The method of Claim 1 wherein the tagged inhibitor of
beta-amyloid production comprises a radiolabeled inhibitor
of beta-amyloid production, a fluorescence labeled
inhibitor of beta-amyloid production or a biotin labeled
inhibitor of beta-amyloid production.
- 30 3. The method of Claim 1 wherein the tagged inhibitor of
beta-amyloid production comprises a radiolabeled inhibitor
of beta-amyloid production.
- 35 4. The method of Claim 1 wherein the tagged inhibitor of
beta-amyloid production comprises a tritium or iodine
radiolabeled inhibitor of beta-amyloid production.

5. The method of Claim 1 wherein the tagged inhibitor of beta-amyloid production comprises a tritium radiolabeled inhibitor of beta-amyloid production.

- 5 6. The method of Claim 1 wherein the tagged inhibitor of beta-amyloid production comprises a compound of the Formula (I):



(I)

wherein:

at least one atom of the compound of the Formula (I) is radiolabeled;

15 Q is NH₂;

R³ is C₁-C₆ alkyl substituted with 0-1 R⁴;

18 R⁴ is H, OH, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₀ carbocycle, C₆-C₁₀ aryl, or 5 to 10 membered heterocycle;

R⁵ is H, OR¹⁴;

20 C₁-C₆ alkyl substituted with 0-3 R^{5b};
 25 C₁-C₆ alkoxy substituted with 0-3 R^{5b};
 C₂-C₆ alkenyl substituted with 0-3 R^{5b};
 C₂-C₆ alkynyl substituted with 0-3 R^{5b};
 C₃-C₁₀ carbocycle substituted with 0-3 R^{5c};
 C₆-C₁₀ aryl substituted with 0-3 R^{5c}; or
 30 5 to 10 membered heterocycle substituted with 0-3 R^{5c};

R^{5b}, at each occurrence, is independently selected from:
 H, C₁-C₆ alkyl, CF₃, OR¹⁴, Cl, F, Br, I, =O, CN, NO₂, NR¹⁵R¹⁶;

35 C₃-C₁₀ carbocycle substituted with 0-3 R^{5c};

C₆-C₁₀ aryl substituted with 0-3 R^{5c}; or
5 to 10 membered heterocycle substituted with 0-3 R^{5c};

5 R^{5c}, at each occurrence, is independently selected from H,
OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl, F, Br, I, CN, NO₂,
NR¹⁵R¹⁶, or CF₃;

R⁶ is H;
C₁-C₆ alkyl substituted with 0-3 R^{6a};
10 C₃-C₁₀ carbocycle substituted with 0-3 R^{6b}; or
C₆-C₁₀ aryl substituted with 0-3 R^{6b};

R^{6a}, at each occurrence, is independently selected from H,
C₁-C₆ alkyl, OR¹⁴, Cl, F, Br, I, =O, CN, NO₂, NR¹⁵R¹⁶,
15 phenyl or CF₃;

R^{6b}, at each occurrence, is independently selected from H,
OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl, F, Br, I, CN, NO₂,
NR¹⁵R¹⁶, or CF₃;

20 W is -(CR⁸R^{8a})_p-;

p is 0 to 4;

25 R⁸ and R^{8a}, at each occurrence, are independently selected
from H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl and
C₃-C₈ cycloalkyl;

X is a bond;
30 C₆-C₁₀ aryl substituted with 0-3 R^{Xb};
C₃-C₁₀ carbocycle substituted with 0-3 R^{Xb}; or
5 to 10 membered heterocycle substituted with 0-3 R^{Xb};

R^{Xb}, at each occurrence, is independently selected from H,
35 OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl, F, Br, I, CN, NO₂,
NR¹⁵R¹⁶, or CF₃;

Y is a bond or -(CR⁹R^{9a})_t-V-(CR⁹R^{9a})_u-;

t is 0 to 3;

u is 0 to 3;

5

R⁹ and R^{9a}, at each occurrence, are independently selected from H, C₁-C₆ alkyl or C₃-C₈ cycloalkyl;

10 V is a bond, -C(=O)-, -O-, -S-, -S(=O)-, -S(=O)₂-, -N(R¹⁹)-, -C(=O)NR^{19b}-, -NR^{19b}C(=O)-, -NR^{19b}S(=O)₂-, -S(=O)₂NR^{19b}-, -NR^{19b}S(=O)-, -S(=O)NR^{19b}-, -C(=O)O-, or -OC(=O)-;

Z is H;

15 C₁-C₈ alkyl substituted with 0-2 R¹²;
C₂-C₄ alkenyl substituted with 0-2 R¹²;
C₂-C₄ alkynyl substituted with 0-2 R¹²;
C₆-C₁₀ aryl substituted with 0-4 R^{12b};
C₃-C₁₀ carbocycle substituted with 0-4 R^{12b}; or
5 to 10 membered heterocycle substituted with 0-3 R^{12b};

20

R¹² is C₆-C₁₀ aryl substituted with 0-4 R^{12b};
C₃-C₁₀ carbocycle substituted with 0-4 R^{12b}; or
5 to 10 membered heterocycle substituted with 0-3 R^{12b};

25 R^{12b}, at each occurrence, is independently selected from H, OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl, F, Br, I, CN, NO₂, NR¹⁵R¹⁶, or CF₃;

30 B is a 5 to 10 membered lactam, wherein the lactam is saturated, partially saturated or unsaturated; wherein each additional lactam carbon is substituted with 0-2 R¹¹; and, optionally, the lactam contains a heteroatom selected from -O-, -S-, -S(=O)-, -S(=O)₂-, -N=, and -N(R¹⁰)-;

35

R¹⁰ is H, C(=O)R¹⁷, C(=O)OR¹⁷, C(=O)NR¹⁸R¹⁹, S(=O)₂NR¹⁸R¹⁹, S(=O)₂R¹⁷;
C₁-C₆ alkyl optionally substituted with R^{10a};

C₆-C₁₀ aryl substituted with 0-4 R^{10b};
C₃-C₁₀ carbocycle substituted with 0-3 R^{10b}; or
5 to 10 membered heterocycle optionally substituted
with 0-3 R^{10b};

5

R^{10a}, at each occurrence, is independently selected from H,
C₁-C₆ alkyl, C₃-C₆ cycloalkyl, OR¹⁴, Cl, F, Br, I, =O,
CN, NO₂, NR¹⁵R¹⁶, phenyl or CF₃;

10 R^{10b}, at each occurrence, is independently selected from H,
OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl, F, Br, I, CN, NO₂,
NR¹⁵R¹⁶, or CF₃;

R¹¹ is C₁-C₄ alkoxy, Cl, F, Br, I, =O, CN, NO₂, NR¹⁸R¹⁹,
15 C(=O)R¹⁷, C(=O)OR¹⁷, C(=O)NR¹⁸R¹⁹, S(=O)₂NR¹⁸R¹⁹, CF₃;
C₁-C₆ alkyl optionally substituted with R^{11a};
C₆-C₁₀ aryl substituted with 0-3 R^{11b};
C₃-C₁₀ carbocycle substituted with 0-3 R^{11b}; or
5 to 10 membered heterocycle substituted with 0-3 R^{11b};

20

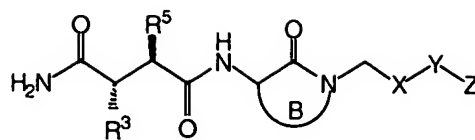
alternatively, two R¹¹ substituents on the same carbon
atoms may be combined to form a C₃-C₆ carbocycle;

alternatively, two R¹¹ substituents on adjacent carbon
25 atoms may be combined to form a C₃-C₆ carbocycle or a
benzo fused radical, wherein said benzo fused radical
is substituted with 0-3 R¹³;

R^{11a}, at each occurrence, is independently selected from H,
30 C₁-C₆ alkyl, OR¹⁴, Cl, F, Br, I, =O, CN, NO₂, NR¹⁵R¹⁶,
phenyl or CF₃;

R^{11b}, at each occurrence, is independently selected from H,
OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl, F, Br, I, CN, NO₂,
35 NR¹⁵R¹⁶, or CF₃;

- R¹³, at each occurrence, is independently selected from H, OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl, F, Br, I, CN, NO₂, NR¹⁵R¹⁶, or CF₃;
- 5 R¹⁴ is H, phenyl, benzyl, C₁-C₆ alkyl, or C₂-C₆ alkoxyalkyl;
- R¹⁵, at each occurrence, is independently selected from H, C₁-C₆ alkyl, benzyl, phenethyl, -C(=O)-(C₁-C₆ alkyl) and -S(=O)₂-(C₁-C₆ alkyl);
- 10 R¹⁶, at each occurrence, is independently selected from H, OH, C₁-C₆ alkyl, benzyl, phenethyl, -C(=O)-(C₁-C₆ alkyl) and -S(=O)₂-(C₁-C₆ alkyl);
- 15 R¹⁷ is H, phenyl, benzyl, C₁-C₆ alkyl, or C₂-C₆ alkoxyalkyl;
- R¹⁸, at each occurrence, is independently selected from H, C₁-C₆ alkyl, benzyl, phenethyl, -C(=O)-(C₁-C₆ alkyl) and -S(=O)₂-(C₁-C₆ alkyl); and
- 20 R¹⁹, at each occurrence, is independently selected from H, OH, C₁-C₆ alkyl, phenyl, benzyl, phenethyl, -C(=O)-(C₁-C₆ alkyl) and -S(=O)₂-(C₁-C₆ alkyl);
- 25 R^{19b} is H, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, phenyl, benzyl or phenethyl; and
- R²⁰ is H or C₁-C₆ alkyl.
- 30 7. The method of Claim 6 wherein R³ is C₃-C₆ alkyl.
8. The method of Claim 6 wherein R³ is C₃-C₆ alkyl substituted with about 1 to about 4 ³H.
- 35 9. The method of Claim 6 wherein the tagged inhibitor of beta-amyloid production comprises a compound of the Formula (II):



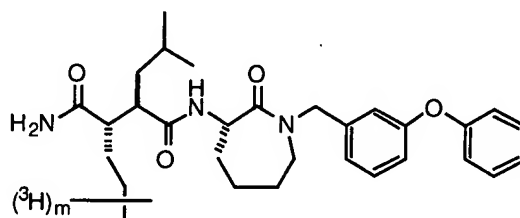
(II)

wherein:

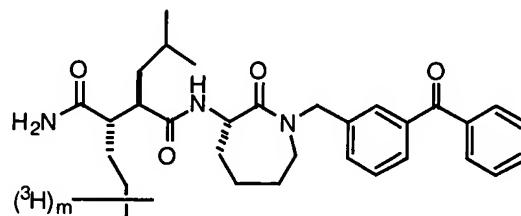
at least one atom of the compound of the Formula (II) is
 5 radiolabeled.

10. The method of Claim 9 wherein R³ is C₃-C₆ alkyl substituted with about 1 to about 4 ³H.

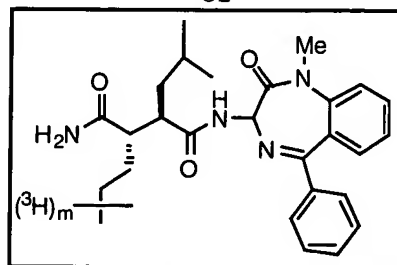
10 11. The method of Claim 1 wherein the tagged inhibitor of beta-amyloid production comprises a compound of Formula:



or

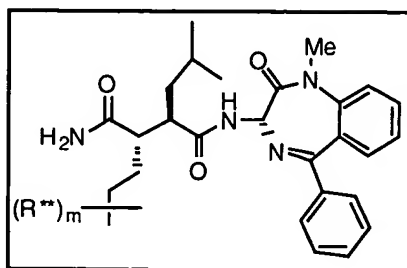


or



wherein m is about 2.

12. The method of Claim 1 wherein the tagged inhibitor of beta-amyloid production comprises a compound of Formula (I-43T):



(I-43T)

wherein m is about 2.

13. The method of Claim 1 wherein at least one macromolecule involved in the processing of APP and the production of beta-amyloid peptide comprises presenilin 1 or a fragment of presenilin 1.

14. The method of Claim 1 wherein at least one macromolecule involved in the processing of APP and/or the production of beta-amyloid peptide comprises:

- (1) presenilin-1;
- (2) presenilin-2;
- (3) β secretase;
- (4) α secretase;
- (5) γ secretase; or
- (6) BACE/memapsin 2;

or any fragment or derivative thereof.

15. The method of Claim 1 wherein the inhibitory concentration is half maximal inhibitory concentration.

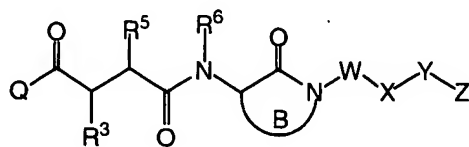
16. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of an inhibitor of beta-amyloid production identified by the screening assay of Claim 1 or a pharmaceutically acceptable salt or prodrug form thereof.

17. A method for treating degenerative neurological disorders involving beta-amyloid production comprising administering to a host in need of such treatment a therapeutically effective amount of an inhibitor of beta-amyloid production identified by the screening assay of Claim 1 or a pharmaceutically acceptable salt or prodrug form thereof.
18. A method for treating Alzheimer's disease comprising administering to a host in need of such treatment a therapeutically effective amount of an inhibitor of beta-amyloid production identified by the screening assay of Claim 1 or a pharmaceutically acceptable salt or prodrug form thereof.
19. A method of identifying a macromolecule involved in APP processing comprising
- 1) contacting a tagged inhibitor of beta-amyloid production with material suspected to contain a macromolecule involved in APP processing;
 - 2) separating a complex comprising a tagged inhibitor of beta-amyloid production and a macromolecule involved in APP processing; and
 - 3) identifying the complex.
20. The method of Claim 19 wherein the tagged inhibitor of beta-amyloid production comprises a radiolabeled inhibitor of beta-amyloid production, a fluorescence labeled inhibitor of beta-amyloid production, a biotin labeled inhibitor of beta-amyloid production, a photoaffinity labeled inhibitor of beta-amyloid production, or any combination of tags thereof in one inhibitor of beta-amyloid production.
21. The method of Claim 19 wherein the tagged inhibitor of beta-amyloid production comprises a radiolabeled inhibitor of beta-amyloid production.

22. The method of Claim 19 wherein the tagged inhibitor of beta-amyloid production comprises a tritium labeled inhibitor of beta-amyloid production.

5

23. The method of Claim 19 wherein the tagged inhibitor of beta-amyloid production comprises a compound of Formula (I):



10

(I)

wherein:

at least one atom of the compound of the Formula (I) is radiolabeled;

15

Q is NH₂;

R³ is C₁-C₆ alkyl substituted with 0-1 R⁴;

20 R⁴ is H, OH, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₀ carbocycle, C₆-C₁₀ aryl, or 5 to 10 membered heterocycle;

R⁵ is H, OR¹⁴;

25

C₁-C₆ alkyl substituted with 0-3 R^{5b};

C₁-C₆ alkoxy substituted with 0-3 R^{5b};

C₂-C₆ alkenyl substituted with 0-3 R^{5b};

C₂-C₆ alkynyl substituted with 0-3 R^{5b};

C₃-C₁₀ carbocycle substituted with 0-3 R^{5c};

30

C₆-C₁₀ aryl substituted with 0-3 R^{5c}; or

5 to 10 membered heterocycle substituted with 0-3 R^{5c};

R^{5b}, at each occurrence, is independently selected from:

H, C₁-C₆ alkyl, CF₃, OR¹⁴, Cl, F, Br, I, =O, CN, NO₂,

35

NR¹⁵R¹⁶;

- C₃-C₁₀ carbocycle substituted with 0-3 R^{5c};
 C₆-C₁₀ aryl substituted with 0-3 R^{5c}; or
 5 to 10 membered heterocycle substituted with 0-3 R^{5c};
- 5 R^{5c}, at each occurrence, is independently selected from H,
 OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl, F, Br, I, CN, NO₂,
 NR¹⁵R¹⁶, or CF₃;
- R⁶ is H;
- 10 C₁-C₆ alkyl substituted with 0-3 R^{6a};
 C₃-C₁₀ carbocycle substituted with 0-3 R^{6b}; or
 C₆-C₁₀ aryl substituted with 0-3 R^{6b};
- 15 R^{6a}, at each occurrence, is independently selected from H,
 C₁-C₆ alkyl, OR¹⁴, Cl, F, Br, I, =O, CN, NO₂, NR¹⁵R¹⁶,
 phenyl or CF₃;
- 20 R^{6b}, at each occurrence, is independently selected from H,
 OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl, F, Br, I, CN, NO₂,
 NR¹⁵R¹⁶, or CF₃;
- W is -(CR⁸R^{8a})_p-;
- p is 0 to 4;
- 25 R⁸ and R^{8a}, at each occurrence, are independently selected
 from H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl and
 C₃-C₈ cycloalkyl;
- 30 X is a bond;
 C₆-C₁₀ aryl substituted with 0-3 R^{Xb};
 C₃-C₁₀ carbocycle substituted with 0-3 R^{Xb}; or
 5 to 10 membered heterocycle substituted with 0-3 R^{Xb};
- 35 R^{Xb}, at each occurrence, is independently selected from H,
 OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl, F, Br, I, CN, NO₂,
 NR¹⁵R¹⁶, or CF₃;

Y is a bond or $-(CR^9R^{9a})_t-V-(CR^9R^{9a})_u-$;

t is 0 to 3;

5 u is 0 to 3;

R^9 and R^{9a} , at each occurrence, are independently selected from H, C_1-C_6 alkyl or C_3-C_8 cycloalkyl;

10 V is a bond, $-C(=O)-$, $-O-$, $-S-$, $-S(=O)-$, $-S(=O)_2-$, $-N(R^{19})-$, $-C(=O)NR^{19b}-$, $-NR^{19b}C(=O)-$, $-NR^{19b}S(=O)_2-$, $-S(=O)_2NR^{19b}-$, $-NR^{19b}S(=O)-$, $-S(=O)NR^{19b}-$, $-C(=O)O-$, or $-OC(=O)-$;

Z is H;

15 C_1-C_8 alkyl substituted with 0-2 R^{12} ;
 C_2-C_4 alkenyl substituted with 0-2 R^{12} ;
 C_2-C_4 alkynyl substituted with 0-2 R^{12} ;
 C_6-C_{10} aryl substituted with 0-4 R^{12b} ;
 C_3-C_{10} carbocycle substituted with 0-4 R^{12b} ; or
20 5 to 10 membered heterocycle substituted with 0-3 R^{12b} ;

R^{12} is C_6-C_{10} aryl substituted with 0-4 R^{12b} ;
 C_3-C_{10} carbocycle substituted with 0-4 R^{12b} ; or
5 to 10 membered heterocycle substituted with 0-3 R^{12b} ;

25

R^{12b} , at each occurrence, is independently selected from H, OH, C_1-C_6 alkyl, C_1-C_4 alkoxy, Cl, F, Br, I, CN, NO_2 , $NR^{15}R^{16}$, or CF_3 ;

30 B is a 5 to 10 membered lactam, wherein the lactam is saturated, partially saturated or unsaturated; wherein each additional lactam carbon is substituted with 0-2 R^{11} ; and, optionally, the lactam contains a heteroatom selected from $-O-$, $-S-$, $-S(=O)-$, $-S(=O)_2-$, $-N=$ and -
35 $N(R^{10})-$;

R^{10} is H, $C(=O)R^{17}$, $C(=O)OR^{17}$, $C(=O)NR^{18}R^{19}$, $S(=O)_2NR^{18}R^{19}$, $S(=O)_2R^{17}$;

C₁-C₆ alkyl optionally substituted with R^{10a};
C₆-C₁₀ aryl substituted with 0-4 R^{10b};
C₃-C₁₀ carbocycle substituted with 0-3 R^{10b}; or
5 to 10 membered heterocycle optionally substituted
5 with 0-3 R^{10b};

R^{10a}, at each occurrence, is independently selected from H,
C₁-C₆ alkyl, C₃-C₆ cycloalkyl, OR¹⁴, Cl, F, Br, I, =O,
CN, NO₂, NR¹⁵R¹⁶, phenyl or CF₃;

10

R^{10b}, at each occurrence, is independently selected from H,
OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl, F, Br, I, CN, NO₂,
NR¹⁵R¹⁶, or CF₃;

15

R¹¹ is C₁-C₄ alkoxy, Cl, F, Br, I, =O, CN, NO₂, NR¹⁸R¹⁹,
C(=O)R¹⁷, C(=O)OR¹⁷, C(=O)NR¹⁸R¹⁹, S(=O)₂NR¹⁸R¹⁹, CF₃;
C₁-C₆ alkyl optionally substituted with R^{11a};
C₆-C₁₀ aryl substituted with 0-3 R^{11b};
C₃-C₁₀ carbocycle substituted with 0-3 R^{11b}; or

20

5 to 10 membered heterocycle substituted with 0-3 R^{11b};

alternatively, two R¹¹ substituents on the same carbon
atoms may be combined to form a C₃-C₆ carbocycle;

25

alternatively, two R¹¹ substituents on adjacent carbon
atoms may be combined to form a C₃-C₆ carbocycle or a
benzo fused radical, wherein said benzo fused radical
is substituted with 0-3 R¹³;

30

R^{11a}, at each occurrence, is independently selected from H,
C₁-C₆ alkyl, OR¹⁴, Cl, F, Br, I, =O, CN, NO₂, NR¹⁵R¹⁶,
phenyl or CF₃;

35

R^{11b}, at each occurrence, is independently selected from H,
OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl, F, Br, I, CN, NO₂,
NR¹⁵R¹⁶, or CF₃;

R¹³, at each occurrence, is independently selected from H, OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl, F, Br, I, CN, NO₂, NR¹⁵R¹⁶, or CF₃;

5 R¹⁴ is H, phenyl, benzyl, C₁-C₆ alkyl, or C₂-C₆ alkoxyalkyl;

R¹⁵, at each occurrence, is independently selected from H, C₁-C₆ alkyl, benzyl, phenethyl, -C(=O)-(C₁-C₆ alkyl) and -S(=O)₂-(C₁-C₆ alkyl);

10

R¹⁶, at each occurrence, is independently selected from H, OH, C₁-C₆ alkyl, benzyl, phenethyl, -C(=O)-(C₁-C₆ alkyl) and -S(=O)₂-(C₁-C₆ alkyl);

15 R¹⁷ is H, phenyl, benzyl, C₁-C₆ alkyl, or C₂-C₆ alkoxyalkyl;

R¹⁸, at each occurrence, is independently selected from H, C₁-C₆ alkyl, benzyl, phenethyl, -C(=O)-(C₁-C₆ alkyl) and -S(=O)₂-(C₁-C₆ alkyl); and

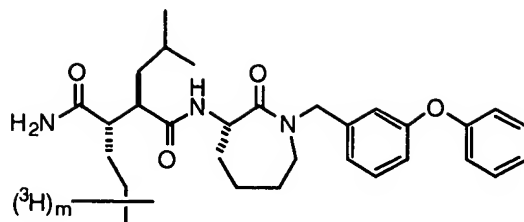
20

R¹⁹, at each occurrence, is independently selected from H, OH, C₁-C₆ alkyl, phenyl, benzyl, phenethyl, -C(=O)-(C₁-C₆ alkyl) and -S(=O)₂-(C₁-C₆ alkyl);

25 R^{19b} is H, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, phenyl, benzyl or phenethyl; and

R²⁰ is H or C₁-C₆ alkyl.

30 24. The method of Claim 19 wherein the tagged inhibitor of beta-amyloid production comprises a compound of the Formula (I-7T):



(I-7T)

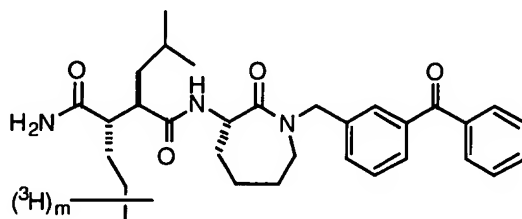
wherein m is about 2.

5

25. The method of Claim 19 wherein the tagged inhibitor of beta-amyloid production comprises a compound of the Formula (I-43T), wherein m is about 2.

10 26. The method of Claim 20 wherein the tagged inhibitor of beta-amyloid production is radiolabeled and photoaffinity labeled.

27. The method of Claim 20 wherein the tagged inhibitor of
15 beta-amyloid production comprises a compound of the Formula (I-11T):



(I-11T)

20

wherein m is about 2.

28. A macromolecule involved in APP processing comprising
a macromolecule to which a tagged inhibitor of beta-amyloid
25 production binds to specifically.

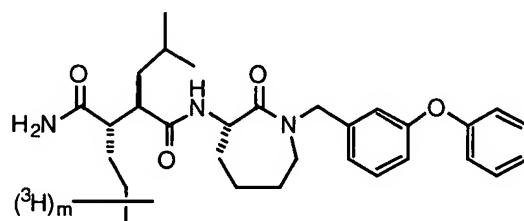
29. A macromolecule of Claim 28 wherein the tagged
inhibitor of beta-amyloid production comprises a
radiolabeled inhibitor of beta-amyloid production, a

fluorescence labeled inhibitor of beta-amyloid production,
a biotin labeled inhibitor of beta-amyloid production, a
photoaffinity labeled inhibitor of beta-amyloid production,
or any combination of tags thereof in one inhibitor of
5 beta-amyloid production.

30. A macromolecule of Claim 28 wherein the tagged
inhibitor of beta-amyloid production comprises a
radiolabeled inhibitor of beta-amyloid production.

10

31. A macromolecule of Claim 28 wherein the tagged
inhibitor of beta-amyloid production comprises a compound
of the Formula (I-7T):

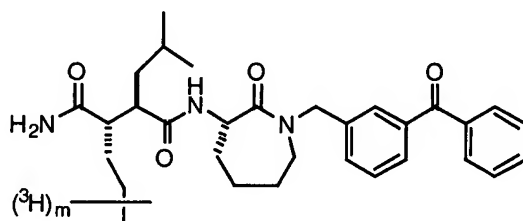


15

(I-7T)

wherein m is about 2.

32. A macromolecule of Claim 28 wherein the tagged
inhibitor of beta-amyloid production comprises a compound
of the Formula (I-11T):

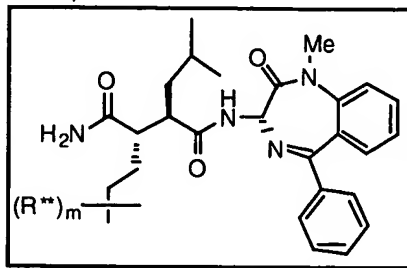


25

(I-11T)

wherein m is about 2.

33. A macromolecule of Claim 28 wherein the tagged inhibitor of beta-amyloid production comprises a compound of the Formula (I-43T):



(I-43T)

wherein m is about 2.

34. The macromolecule of Claim 28 comprising presenilin 1 or a fragment of presenilin 1.

35. The macromolecule of Claim 28 comprising presenilin 2 or a fragment of presenilin 2.

36. An inhibitor of beta-amyloid production comprising a compound which interacts with a binding site on a macromolecule involved in the production of beta-amyloid peptide; wherein said binding site is a specific binding site for a compound of Formula (I-7T) or (I-43T) wherein m is about 2.

37. An inhibitor of beta-amyloid production of Claim 36 wherein the macromolecule involved in the production of beta-amyloid peptide is presenilin 1 or a fragment of presenilin 1.

38. An inhibitor of beta-amyloid production of Claim 36 wherein the macromolecule involved in the production of beta-amyloid peptide is presenilin 2 or a fragment of presenilin 2.

39. An inhibitor of beta-amyloid production of Claim 36 comprising a compound which interacts with a binding site on a macromolecule involved in the production of beta-

amyloid peptide; wherein said binding site is a specific binding site for a compound of Formula (I-7T) wherein m is about 2; and the compound demonstrates a half maximal inhibitory concentration less than 10 micromolar for beta-amyloid production.

40. An inhibitor of beta-amyloid production of Claim 36 comprising a compound which interacts with a binding site on presenilin 1 or a fragment of presenilin 1; wherein said binding site is a specific binding site for a compound of Formula (I-7T) wherein m is about 2; and the compound demonstrates a half maximal inhibitory concentration less than 10 micromolar for beta-amyloid production.

41. An inhibitor of beta-amyloid production of Claim 36 comprising a compound which interacts with a binding site on a macromolecule involved in the production of beta-amyloid peptide; wherein said binding site is a specific binding site for a compound of Formula (I-43T) wherein m is about 2; and the compound demonstrates a half maximal inhibitory concentration less than 10 micromolar for beta-amyloid production.

42. An inhibitor of beta-amyloid production of Claim 36 comprising a compound which interacts with a binding site on presenilin 1 or a fragment of presenilin 1; wherein said binding site is a specific binding site for a compound of Formula (I-43T) wherein m is about 2; and the compound demonstrates a half maximal inhibitory concentration less than 10 micromolar for beta-amyloid production.

43. A tagged inhibitor of beta-amyloid production comprising a tagged compound which interacts with a binding site on a macromolecule involved in the production of beta-amyloid peptide; wherein said binding site is a specific binding site for a compound of Formula (I-7T) or (I-43T) wherein m is about 2.

44. A tagged inhibitor of beta-amyloid production of Claim 43 wherein the macromolecule involved in the production of beta-amyloid peptide is presenilin 1 or a fragment of presenilin 1.

5

45. A tagged inhibitor of beta-amyloid production of Claim 43 wherein the macromolecule involved in the production of beta-amyloid peptide is presenilin 2 or a fragment of presenilin 2.

10

46. A tagged inhibitor of beta-amyloid production of Claim 43 comprising a tagged compound which interacts with a binding site on a macromolecule involved in the production of beta-amyloid peptide; wherein said binding site is a specific binding site for a compound of Formula (I-7T) wherein m is about 2; and the tagged compound demonstrates a half maximal inhibitory concentration less than 10 micromolar for beta-amyloid production.

15

47. A tagged inhibitor of beta-amyloid production of Claim 43 comprising a tagged compound which interacts with a binding site on presenilin 1 or a fragment of presenilin 1; wherein said binding site is a specific binding site for a compound of Formula (I-7T) wherein m is about 2; and the tagged compound demonstrates a half maximal inhibitory concentration less than 10 micromolar for beta-amyloid production.

20

25

48. A tagged inhibitor of beta-amyloid production of Claim 43 comprising a tagged compound which interacts with a binding site on a macromolecule involved in the production of beta-amyloid peptide; wherein said binding site is a specific binding site for a compound of Formula (I-43T) wherein m is about 2; and the tagged compound demonstrates a half maximal inhibitory concentration less than 10 micromolar for beta-amyloid production.

30

35

49. A tagged inhibitor of beta-amyloid production of Claim 43 comprising a tagged compound which interacts with a binding site on presenilin 1 or a fragment of presenilin 1; wherein said binding site is a specific binding site for a compound of Formula (I-43T) wherein m is about 2; and the tagged compound demonstrates a half maximal inhibitory concentration less than 10 micromolar for beta-amyloid production.
50. A method of identifying inhibitors as therapeutics for neurological and other disorders involved in APP processing and beta-amyloid production comprising
- (1) contacting at least one macromolecule involved in APP processing and beta-amyloid production, which macromolecule a tagged inhibitor of beta-amyloid production binds to specifically, with a potential beta-amyloid inhibitor; and
 - (2) determining the level of inhibition of APP processing and beta-amyloid production.
51. The method of Claim 50 wherein the macromolecule is a complex of macromolecules.
52. The method of Claim 50 wherein the macromolecule is presenilin 1 or a fragment of presenilin 1.
53. The method of Claim 50 wherein the macromolecule is presenilin 2 or a fragment of presenilin 2.
54. A method of treating Alzheimer's disease comprising administering to a host in need of such treatment a therapeutically effective amount of an inhibitor of beta-amyloid production, or a pharmaceutically acceptable salt or prodrug form thereof, wherein said inhibitor of beta-amyloid production binds to a binding site on a macromolecule involved in the production of beta-amyloid peptide and effects a decrease in production of beta-amyloid peptide;

wherein said binding site is a specific binding site for a compound of Formula (I-7T) or (I-43T) wherein m is about 2.

55. The method of Claim 54 wherein the macromolecule
5 comprises presenilin-1, a fragment of presenilin-1,
presenilin-2, or a fragment of presenilin-2.

56. A method of Claim 54 wherein the binding site is a
specific binding site for a compound of Formula (I-43T)
10 wherein m is about 2.

57. The method of Claim 56 wherein the macromolecule
comprises presenilin-1 or a fragment of presenilin-1.

15 58. The method of Claim 56 wherein the macromolecule
comprises presenilin-2 or a fragment of presenilin-2.

59. A method of in vivo diagnostic imaging comprising
20 administering to a subject a diagnostically effective
amount of a radiolabeled inhibitor of beta-amyloid
production.

60. A method of Claim 59 wherein said method is used in
25 the diagnosis of a neurological disease which involves APP
processing or elevated levels of beta-amyloid, or both.

61. A method of Claim 59 wherein said method is used in
the diagnosis of Alzheimer's disease.
30

62. A method of Claim 59 wherein the radiolabeled
inhibitor is suitable for imaging of the brain of the
subject.

35 63. A method of Claim 59 wherein the radiolabeled
inhibitor is radiolabeled with one or more radioisotope
selected from ^3H , ^{11}C , ^{14}C , ^{18}F , ^{32}P , ^{35}S , ^{123}I , ^{125}I , or
 ^{131}I .

64. A method of Claim 59 wherein the inhibitor of
beta-amyloid production is a compound selected from any
compound disclosed in or within the scope of compounds
5 disclosed in a reference selected from:

- (1) United States patent US 5,703,129;
- (2) PCT application WO98/22441 (or its priority USSN
08/755,444);
- 10 (3) PCT application WO98/22433 (or its priority USSN
08/807,538);
- (4) PCT application WO98/22430 (or its priority USSN
08/754,895);
- (5) PCT application WO98/22493 (or its priority USSN
15 08/755,334);
- (6) PCT application WO98/22494 (or its priorities USSN
08/808,528, 08/807,528 or 08/807,427);
- (7) PCT application WO98/28268 (or its priority USSN
08/780,025);
- 20 (8) PCT application WO98/38177;
- (9) PCT application WO95/09838
- (10) PCT application WO99/67221;
- (11) PCT application WO99/67220;
- (12) PCT application WO99/67219;
- 25 (13) PCT application WO95/66934;
- (14) PCT application WO00/24392; or
- (15) Ghosh et al., JACS (2000) 122:3522-2523;

or any compound which inhibits beta-amyloid production and
30 binds competitively with any of the foregoing compounds in
any of the assays described in the Utility section hereof;

all of which foregoing references are hereby incorporated
by reference in their entirety.

35

65. A method of Claim 59 wherein the inhibitor of
beta-amyloid production exhibits activity as an inhibitor
in the method of any of Claim 1.

- 5 66. A method of Claim 59 wherein the inhibitor of
beta-amyloid production binds to a macromolecule which is
capable of being identified by the method of any of Claim
19.
- 10 67. A method of Claim 59 wherein the inhibitor of
beta-amyloid production binds to a macromolecule of any of
Claim 28.
68. A method of Claim 59 wherein the inhibitor of
beta-amyloid production is selected from an inhibitor of
any of Claim 36.
- 15 69. A method of Claim 59 wherein the radiolabeled
inhibitor of beta-amyloid production is a radiolabeled
tagged inhibitor of any of Claims 43.
- 20 70. A method of Claim 59 wherein the inhibitor of
beta-amyloid production is selected from:
 (1) an inhibitor of presenilin-1;
 (2) an inhibitor of presenilin-2;
 (3) an inhibitor of β secretase;
 (4) an inhibitor of α secretase;
25 (5) an inhibitor of γ secretase; or
 (6) an inhibitor of BACE/memapsin 2.
- 30 71. A pharmaceutical composition suitable for in vivo
diagnostic imaging comprising a radiolabeled inhibitor of
beta-amyloid production.
72. A pharmaceutical composition of Claim 71 wherein the
composition is used in the diagnosis of a neurological
disease which involves APP processing or elevated levels of
35 beta-amyloid, or both.

73. A pharmaceutical composition of Claim 71 wherein the composition is used in the diagnosis of Alzheimer's disease.

5 74. A pharmaceutical composition of Claim 71 wherein the radiolabeled inhibitor is suitable for imaging of the brain of the subject.

75. A pharmaceutical composition of Claim 71 wherein the
10 radiolabeled inhibitor is radiolabeled with one or more radioisotope selected from ^3H , ^{11}C , ^{14}C , ^{18}F , ^{32}P , ^{35}S , ^{123}I , ^{125}I , or ^{131}I .

76. A pharmaceutical composition of Claim 71 wherein the
15 inhibitor of beta-amyloid production is a compound selected from any compound disclosed in or within the scope of compounds disclosed in a reference selected from:

- (1) United States patent US 5,703,129;
- 20 (2) PCT application WO98/22441 (or its priority USSN 08/755,444);
- (3) PCT application WO98/22433 (or its priority USSN 08/807,538);
- (4) PCT application WO98/22430 (or its priority USSN
25 08/754,895);
- (5) PCT application WO98/22493 (or its priority USSN 08/755,334);
- (6) PCT application WO98/22494 (or its priorities USSN 08/808,528, 08/807,528 or 08/807,427);
- 30 (7) PCT application WO98/28268 (or its priority USSN 08/780,025);
- (8) PCT application WO98/38177;
- (9) PCT application WO95/09838;
- (10) PCT application WO99/67221;
- 35 (11) PCT application WO99/67220;
- (12) PCT application WO99/67219;
- (13) PCT application WO95/66934;
- (14) PCT application WO00/24392; or

(15) Ghosh et al., JACS (2000) 122:3522-2523;

or any compound which inhibits beta-amyloid production and
binds competitively with any of the foregoing compounds in
5 any of the assays described in the Utility section hereof;

all of which foregoing references are hereby incorporated
by reference in their entirety.

10 75. A pharmaceutical composition of Claim 71 wherein the
inhibitor of beta-amyloid production is selected from:

- (1) an inhibitor of presenilin-1;
- (2) an inhibitor of presenilin-2;
- (3) an inhibitor of β secretase;
- 15 (4) an inhibitor of α secretase;
- (5) an inhibitor of γ secretase; or
- (6) an inhibitor of BACE/memapsin 2.